Claim 21 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Without admitting the propriety of the rejection and reserving the right to pursue this claim at a later date, Claim 21 has been cancelled. Applicants respectfully request withdrawal of the rejection.

Claims 22-27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 22-27 have been cancelled. Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 102(b)

Claims 21-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Hardman, U.S. Patent No. 4,939,666. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 21-26 have been cancelled making the rejection moot. Applicants respectfully request the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejection under 35 U.S.C. § 103 (a)

Claims 22 and 27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hardman in view of Lee, et al., U.S. Patent No. 5,241,470. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 22 and 27 have been cancelled making the rejection moot. Applicants respectfully request the rejection of Claims 22 and 27 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Double Patenting Rejections

37 C.F.R. 1.75

Claims 29-50 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 2-20. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 2-20 have been cancelled, thus the objection is moot.

Claims 29-33 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 2-6. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 2-6 have been cancelled, thus the objection is moot.

Claims 34, 49 and 50 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 7. Without admitting the propriety of the rejection and reserving the right

to pursue these claims at a later date, Claims 7, 49 and 50 have been cancelled, thus the objection is moot.

Claims 35-37 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 8-10. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 8-10 have been cancelled, thus the objection is moot.

Claims 39-48 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 11-20. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 11-20 have been cancelled, thus the objection is moot.

In light of the above cancellations, Applicants respectfully request withdrawal of the objection.

35 U.S.C. §101

Claims 22-27 are provisionally rejected under 35 USC 101 as claiming the same invention as that of claims 22-27 of co-pending Application 09/714,357. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 22-27 have been cancelled. Applicants respectfully request withdrawal of the rejection.

Claims 2-5, 7-16, 28-32, 34-37, 39-44, 49 and 50 are rejected under 35 USC 101 as claiming the same invention as that of claims 1-15 of prior U.S. Patent No. 6,188,965. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 2-5, 7-16, 49 and 50 have been cancelled, thus the rejection is moot as applied to these claims.

A statutory double patenting rejection is proper if the claims of an application are directed to the "same invention" as the claims in a patent that has already been granted to the Applicants, or that are in a co-pending application. *In re Vogel* states that:

> By "same invention" we mean identical subject matter. Thus the invention defined by a claim reciting "halogen" is not the same as that defined by a claim reciting "chlorine," because the former is broader than the latter.... A good test, and probably the only objective test, for "same invention," is whether one of the claims could be literally infringed without literally infringing the other. If it could be, the claims do not define identically the same invention.

Claims 28-32, 34-37, and 39-44 are not identical to cited Claims 1-15 of U.S. Patent No. 6,188,965 because they are directed to altering "amino acids" in contrast with "rotamers." As defined in the specification at page 7, lines 13-14, these are distinct:

> Each amino acid can be represented by a discrete set of all allowed conformers of each side chain, called rotamers.

Accordingly, Applicants respectfully withdrawal of the rejection of claims 28-32, 34-37, and 39-44 based on double patenting with U.S. Patent No. 6,188,965.

Non-statutory Double Patenting

Claims 2, 6, 17-20 28, 29, 33, 28, and 45-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6, 11, and 18-21 of U.S. Patent No. 6,269,312. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 2, 6, and 17-20 have been cancelled; the rejection is moot as applied to these claims.

Applicants are in the process of preparing a terminal disclaimer for claims 28, 29, 33, 28, and 45-48 and will forward it to the Examiner once a signed copy is obtained from the assignee.

The Applicants submit that in light of the above-amendment and argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the claims by the "Amendment". The attached page is captioned **"Version with markings to show changes made."**

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Dated: 11/25/02

Respectfully submitted,
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Version with Markings to Show Changes Made

In the Claims:

Claim 29 has been amended as shown below:

29. (Once Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) classifying each variable residue position as either a core, surface or boundary residue;

(C) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue positions has an amino acid selected from each of at least two different amino acids; and

(D) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences.

Claim 30 has been amended as shown below:

30. (Once Amended) A method according to claim 29, 51 or 52 wherein said analyzing step comprises a DEE computation.

Claim 31 has been amended as shown below:

31. (Once Amended) A method according to claim [28 or 29] 28, 29, 51 or 52 wherein said set of optimized protein sequences comprises the globally optimal protein sequence.

Claim 33 has been amended as shown below:

33. (Once Amended) A method according to claim [28 or 29] 28, 29, 51 or 52 wherein said analyzing step includes the use of at least one scoring function.

Claim 34 has been amended as shown below:

34. (Once Amended) A method according to claim 33 wherein said scoring function is selected from the group consisting of a [Van] van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

Claim 39 has been amended as shown below:

39. (Once Amended) A method according to claim [28 or 29] 28, 29, 51 or 52further comprising experimentally testing at least one member of said set.

Claim 40 has been amended as shown below:

40. (Once Amended) A method according to claim 31 further comprising the step of: generating a [rank ordered] list of additional optimal sequences from said globally optimal protein sequence.

Claim 42 has been amended as shown below:

42. (Once Amended) A method according to claim 29, 51 or 52 wherein said analyzing step comprises a Monte Carlo computation.

Claim 43 has been amended as shown below:

43. (Once Amended) A method according to claim 40 further comprising the step of: testing some or all of said protein sequences from said [ordered] list to produce potential energy test results.

Claim 45 has been amended as shown below:

45. (Once Amended) A recombinant protein comprising an optimized protein sequence generated by the method of claim [28 or 29] 28, 29, 51 or 52.

Claims 49 and 50 have been cancelled.

Appendix of Pending Claims

28. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) establishing a group of potential amino acids for each of said variable residue positions; and

(C) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized proteins sequences, wherein said analyzing step includes a Dead-End Elimination (DEE) computation.

29. (Once Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) classifying each variable residue position as either a core, surface or boundary residue;

(C) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue positions has an amino acid selected from each of at least two different amino acids; and

(D) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences.

30. (Once Amended) A method according to claim 29, 51 or 52 wherein said analyzing step comprises a DEE computation.

31. (Once Amended) A method according to claim 28, 29, 51 or 52 wherein said set of optimized protein sequences comprises the globally optimal protein sequence.

32. A method according to claim 28 or 30 wherein said DEE computation is selected from the group consisting of original DEE and Goldstein DEE.

33. (Once Amended) A method according to claim 28, 29, 51 or 52 wherein said analyzing step includes the use of at least one scoring function.

34. A method according to claim 33 wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

35. A method according to claim 33 wherein said analyzing step includes the use of at least two scoring functions.

36. A method according to claim 33 wherein said analyzing step includes the use of at least three scoring functions.

37. A method according to claim 33 wherein said analyzing step includes the use of at least four scoring functions.

38. A method according to claim 33 wherein said atomic solvation scoring function includes a scaling factor that compensates for over-counting.

39. (Once Amended) A method according to claim 28, 29, 51 or 52 further comprising experimentally testing at least one member of said set.

40. (Once Amended) A method according to claim 31 further comprising the step of: generating a list of additional optimal sequences from said globally optimal protein sequence.

41. A method according to claim 40 wherein said generating includes the use of a Monte Carlo search.

42. (Once Amended) A method according to claim 29, 51, or 52 wherein said analyzing step comprises a Monte Carlo computation.

43. (Once Amended) A method according to claim 40 further comprising the step of: testing some or all of said protein sequences from said list to produce potential energy test results.

44. A method according to claim 43 further comprising the step of:
analyzing the correspondence between said potential energy test results and theoretical potential energy data.

45. (Once Amended) A recombinant protein comprising an optimized protein sequence generated by the method of claim 28, 29, 51 or 52.

46. A nucleic acid sequence encoding a recombinant protein according to claim 45.

47. An expression vector comprising nucleic acid sequence of claim 46.

48. A host cell comprising the nucleic acid sequence of claim 46.

51. (New) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) establishing a group of potential amino acids for each of said variable residue positions; and

(C) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences.

52. (New) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue positions has an amino acid selected from each of at least two different amino acids; and

(C) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences.